CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022406Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	(electronic stamp)
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
NDA/BLA #	22406/S000
Applicant Name	Janssen Pharmaceuticals, Inc.
Date of Submission	1/04/11
PDUFA Goal Date	7/03/11
Proprietary Name /Established (USAN) Name	Xarelto/rivaroxaban
Dosage Forms / Strength	Oral Tablets/10 mg film-coated
Proposed Indication(s)	For the prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip replacement surgery or knee replacement surgery
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Division Director	Ann T. Farrell, MD, Acting Division Director
Medical Officer Review	Min Lu, M.D./Kathy Robie-Suh, M.D./Ph.D.
Statistical Review	Qing Xu, Ph.D./Mark Rothmann, Ph.D.
Pharmacology Toxicology Review	Yash Chopra, PhD./Adebayo Laniyonu, Ph.D. and Patricia Harlow, PhD./ Thomas Papoian, Ph.D.
CMC Review/OBP Review	Joyce Crich, Ph.D./Janice Brown, Ph.D. and Tapash Ghosh, Ph.D./Patrick Marroum, Ph.D.
Microbiology Review	N/A
Clinical Pharmacology Review	Joseph Grillo, Ph.D./Julie Bullock, Ph.D.
DDMAC	James Dvorsky
DSI	Susan Thompson, M.D./Tejashari Purohit Sheth, M.D./Leslie Ball, M.D.
CDTL Reviews	Kathy Robie-Suh, M.D., Ph.D.
OSE/DMEPA	Denise V. Baugh, PharmD, BCPS/Carol Holquist, RPh
OSE/Epidemiology	Kate Gelperin, M.D./John Senior, M.D.
Other - statistical safety	John Yap, Ph.D./ LaRee Tracy, Ph.D./Aloka Chakravarty, Ph.D.
Other – Pediatrics Maternal Health Team Other- Pharmacometrics	Elizabeth L. Durmowicz, M.D./Hari C. Sachs, M.D./Lisa Mathis, M.D. Dr. Upasana Bhatnagar, MD/ Karen Feibus, M.D./ Lisa Mathis, M.D. Nitin Mehrotra, Ph.D./Christine Garnett, Ph.D.

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology

1. Introduction

Xarelto is an oral Factor Xa inhibitor initially submitted on July 22, 2008 for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip replacement surgery or knee replacement surgery. On May 27, 2009, a complete response letter was issued in the first cycle due to the need to clarify chemistry, manufacturing and control (CMC) issues; need for additional understanding of potential safety issues; and need for additional clarification of data integrity issues. The applicant responded to the complete response letter on January 4, 2011.

Xarelto has been approved by the European Medicines Agency since May 6, 2009.

2. Background

Four drugs are approved in the prevention of venous thromboembolism (VTE) in the setting of hip and/or knee replacement surgery. All these drugs are administered parenterally (enoxaparin, fondaparinux, dalteparin and unfractionated heparin). Warfarin is the only oral anticoagulant approved for the prophylaxis of venous thrombosis and PE in general. However, warfarin is not specifically indicated for the prevention of VTE in the perioperative period but is widely used.

Unlike warfarin, rivaroxaban does not require anticoagulation parameter monitoring of the prothrombin time (PT). However, rivaroxaban does prolong the partial thromboplastin time (PT) and partial thromboplastin time (PTT).

The original submission had four major trials submitted (RECORD 1, 2, 3, and 4) in support of the application. The first-cycle review team determined the trials supported an efficacy determination; however, a number of deficiencies were identified in the areas of CMC, clinical safety and data integrity. Therefore, a complete response letter was issued.

3. CMC/Device

The CMC reviewers recommend approval of this NDA and state:

"From a Chemistry, Manufacturing and Controls standpoint, this NDA is recommended for approval a 30 month shelf life for the drug product in HDPE bottles and a 18 month shelf life for the drug product in blisters, when stored at 20°-25°C (68°F - 77°F) or room temperature; excursions permitted to 15°C - 30°C (59°F - 86°F) [see USP Controlled Room Temperature]".

4. Nonclinical Pharmacology/Toxicology

The first cycle review did not identify any issues that would preclude approval from a nonclinical standpoint. In the 2-year carcinogenicity studies in CD-1 Mice and Wistar rats, a slight increase in tumors was noted in the Wistar rats study; however, this increase was not statistically significant. The observed increase does not affect the approvability of this NDA which is for short-term use.

5. Clinical Pharmacology/Biopharmaceutics

The recommended dose is 10 mg per day with or without food. Dose modification is suggested if used with a strong P-gp and CYP3A4 inducer.

There are no issues which would preclude approval of rivaroxaban based on the clinical pharmacology reviews. However, the clinical pharmacology review team is recommending additional post-marketing commitment (PMC) and requirements (PMR) to develop a lower dose of rivaroxaban and to evaluate the effect of renal impairment with the concurrent use of P-gp and moderate inhibitors of CYP3A4 on the PK, PD and safety of rivaroxaban (please refer to the action letter for these PMCs/PMRs).

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

During the first cycle review, the primary concerns regarding this application were safety (not efficacy) with a specific concern that there was insufficient safety information on hepatotoxicity to assess the full-risk benefit profile.

From Dr. Lu's first cycle review, *"Four multi-center, randomized controlled trials (RECORD 1-4) were conducted... RECORD 1 and 2 studies were conducted in patients undergoing hip replacement surgery (THR) and RECORD 3 and 4 studies were in patients undergoing knee replacement surgery (TKR).*

In all 4 RECORD trials, rivaroxaban 10 mg once daily administered orally at least 6 to 8 hours after surgery was compared with enoxaparin administered subcutaneously. The enoxaparin dosing regimen was 40mg once daily starting 12 hours preoperatively in RECORD 1-3 studies and was 30 mg twice daily starting 12 to 24 hours postoperatively in RECORD 4 study. The durations of active treatment for rivaroxaban and enoxaparin were similar in the RECORD studies with the exception of RECORD 2, in which treatment duration of Rivaroxaban was much longer than enoxaparin control (rivaroxaban 35 days versus enoxaparin 13 days). The dose regimen of enoxaparin (40 mg once daily) control in RECORD 3 study is not a recommended dose regimen of enoxaparin for the prophylaxis of DVT in patients undergoing TKR in the United States.

Altogether a total of 12,729 patients (6356 in the rivaroxaban group and 6373 in the enoxaparin group were randomized in 4 RECORD studies and 8,512 (67%) (4248 in the rivaroxaban group and 4264 in the enoxaparin group) were included in the Modified Intent to Treat (MITT) population for the primary efficacy analysis. About 30-39% of randomized patients in RECORD studies were excluded from MITT population mainly due to no adequate assessment of DVT.

The primary efficacy endpoint was a composite endpoint of total VTE consisting of any DVT (proximal and/or distal), non-fatal PE, or death from all causes at the end of treatment in all 4 RECORD studies.

The statistical analyses supporting approval from the statistical team's review are in the table below.

Table 1. Summary of Primary Efficacy Endpoint Analysis Results (Total VTE)

Study	Rivaroxaban % (n/N)	Enoxaparin % (n/N)	Absolute Risk Reduction	p-value
RECORD 1	1.1% (18/1595)	3.7% (58/1558)	2.6%	p<0.0001
RECORD 2	2.0% (17/864)	9.3% (81/869)	7.3%	p<0.0001
RECORD 3	9.6% (79/824)	18.9% (166/878)	9.3%	p<0.0001
RECORD 4	6.9% (67/965)	10.1% (97/959)	3.2%	p=0.012

The Division of Scientific Investigations (DSI) identified some problematic sites and investigators during inspection and assessment. Thus, the statistical review team also performed sensitivity analyses excluding the known unreliable sites. The statistical review team reanalyzed the data removing these sites where there were drug accountability and other issues. For each RECORD trial, the sensitivity analysis using the modified ITT population demonstrates a statistically significant difference in favor of rivaroxaban for the primary endpoint. The results are provided in table 2 below.

Table 2. Summary of Primary Efficacy Endpoint Analysis Results (Total VTE) Excluding Unreliable Sites

Study	Rivaroxaban % (n/N)	Enoxaparin % (n/N)	Absolute Risk Reduction	p-value
RECORD 1	1.1% (17/1513)	3.9% (57/1473)	2.8%	p<0.0001
RECORD 2	2.1% (17/828)	8.4% (70/830)	6.3%	p<0.0001
RECORD 3	9.7% (79/813)	18.8% (164/871)	9.1%	p<0.0001
RECORD 4	7.1% (53/742)	10.8% (79/731)	3.7%	p=0.0174

Removing the problematic investigators/sites suggested that the results are still supportive of efficacy claims. However, the Agency has additional concerns regarding the study conduct and data collected in RECORD 4 which are discussed later.

8. Safety

During the first review cycle, the review team identified areas for rigorous safety review: bleeding events, cardiovascular events, hepatotoxicity, and renal toxicity.

Bleeding Events:
Review of the bleeding events revealed an increase in major bleeding events for the rivaroxaban treated patients; however, the difference was not statistically significant.

Cardiovascular Events:
No statistically significant differences were noted between treatment groups during treatment. However, a slightly higher incidence of ischemic stroke was noted after subjects stopped rivaroxaban treatment. The significance of this increase is unclear.

Hepatotoxicity:
The greatest concern during the first cycle review was for hepatotoxicity. The review team requested additional long term follow-up data from the ROCKET studies where rivaroxaban was used for stroke prophylaxis in patients with atrial fibrillation. The longer term data did not reveal a significantly different liver toxicity profile compared with warfarin and enoxaparin.

Renal toxicity:
There were slightly higher incidences of creatinine and urea elevations in the rivaroxaban-treated subjects compared with the active control subjects.

In the second cycle, Dr. Lu concluded:

"The other adverse events reported more frequently with rivaroxaban as compared to the control were pruritus, wound healing complications, pain in extremity, increased muscle tone and cramping, wound secreation, blister, syncope, and dysuria in clinical trials. Other significant adverse events reported associated with rivaroxaban treatment in post-marketing spontaneous reports were cerebral hemorrhage, epidural hematoma, hypersensitivity reactions including anaphylactic shock, agranulocytosis, and Steven-Johnson syndrome".

There is a lack of knowledge about a method to reverse anticoagulation (including excessive anticoagulation). The division will request from the sponsor a method to amass cases of major bleeding seen post-approval, collect information on rivaroxaban dosing, outcome of major bleeding, and any treatment for the major bleeding.

I concur with the conclusions of the clinical and statistical review teams.

9. Advisory Committee Meeting

This product was discussed at a Cardiovascular and Renal Advisory Committee meeting on March 19, 2009. The Committee voted 15 (yes) to 2 (no) that the available clinical data demonstrate a favorable risk-benefit profile.

10. Pediatrics

The applicant requested a full waiver and the pediatric review committee concurred.

11. Other Relevant Regulatory Issues

Maternal Health was consulted and provided labeling recommendations which were incorporated into labeling.

OSE was consulted including DMEPA who provided labeling input.

Division of Scientific Investigation (DSI)
In the May 2009 Complete Response letter, DSI identified items from their initial investigation and inspections that were reviewed in this second-cycle review. Based on the applicant's responses, DSI believes that the data from RECORD trials 1, 2, and 3 are reliable but the data from RECORD 4 are not reliable. The data integrity concerns for RECORD 4 involve the following areas:

1. Post-operative Randomization: DSI inspection discovered that some patients in the RECORD trials were post-operatively randomized to a particular treatment group. Based on the inspection, the percentage of patients was less than 1% for the RECORD trials 1, 2, and 3. However, for RECORD 4 this percentage was approximately 39%. Despite the high percentage of post-operative randomization, post-operative randomization is unlikely to have introduced any bias in favor of rivaroxaban over enoxaparin for efficacy or safety.

2. Unreported Adverse Events: All four RECORD trials had unreported adverse events. The trial with the highest number of unreported adverse events was RECORD 4. In the Falcon audit, RECORD 4 trial had 265 unreported adverse events. In the Parexel audit, RECORD 4 trial had 504 unreported adverse events. The applicant analyzed the safety data including and excluding RECORD 4 data and the percentages for each adverse event/reaction did not change significantly.

3. Drug Accountability Issues: Drug accountability issues were identified in 27-33% of the audited sites. These issues were observed for all RECORD trials.

4. Inadequate Monitoring: DSI inspection of Bayer did uncover problems with the monitoring of the 4 RECORD trials. An inspection of Johnson & Johnson did not uncover similar problems.

Conclusion
While DSI had some concerns regarding each of the RECORD trials, the RECORD 4 trial had significantly more numerous and severe study conduct, oversight and data collection issues. Given the totality of concerns with RECORD 4, Dr. Farrell concluded that the RECORD 4 information appears unreliable and cannot be used for an approval decision.

In summary, RECORD 1 and 2 trials provide the support for the use of rivaroxaban in patients undergoing hip replacement surgery. The RECORD 3 trial which demonstrated the rivaroxaban's efficacy for prevention of VTE in patients undergoing knee replacement surgery is heavily supported by the RECORD 1 and 2 trials and to an uncertain extent by the RECORD 4 trial.

12. Labeling

The labeling was reviewed by all disciplines and consultant staff.

13. Decision/Action/Risk Benefit Assessment

Recommended regulatory action: Approval.

Risk Benefit Assessment:
The risk benefit assessment suggests that oral rivaroxaban is effective for the prophylaxis of venous thrombembolic events in patients undergoing elective hip or knee replacement surgery. The most common side effects include post-operative bleeding.

Recommendation for Postmarketing Risk Management Activities:
Routine postmarketing surveillance except for enhanced pharmacovigilance for major bleeding events.

Recommendation for other Postmarketing Study Requirements (PMR)/Commitments (PMC):
Please refer to the action letter.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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07/01/2011

RICHARD PAZDUR
07/01/2011